REMARKS

Claims 1, 6-7, 20-21, 23-26 and 35-36 are pending after entry of this paper. Claims 1, 6-7, 20-21, 23-26 and 35-36 have been rejected. Claims 2-5, 8-19, 22 and 27-34 have been cancelled without prejudice. Applicants reserve the right to pursue cancelled claims in a continuing application.

Claim 1 has been amended to replace the phrase "a region containing a promoter of the human calponin gene comprising the nucleotide sequence of Seq. ID No.: 1" with the phrase "a region containing a full-length promoter of the human calponin gene" Support may be found throughout the instant specification and claims, for instance, claim 35 as originally filed. Claim 1 has been further amended to clarify the components of the DNA fragment, *i.e.*, the ICP4 gene, the LacZ gene, the EGFP gene, and the region containing a promoter of the human calponin gene. Support may be found throughout the instant specification and claims.

Claims 1 and 35 have been amended to replace the phrase "a DNA that encodes a desired protein linked downstream of the ICP4 gene" with the phrase "the EGFP gene linked to the downstream of the ICP4 gene via an internal ribosomal entry site." Claims 1 and 35 have been further amended to replace the phrase "expresses the desired protein under the control of said region containing a promoter of the human calponin gene" with the phrase "the LacZ gene which is integrated upstream of said region containing a promoter of the human calponin gene." Support for these amendments may be found throughout the instant specification, *e.g.*, page 12, lines 18-26, page 12, line 29 – page 13, line 10, where EGFP is Enhanced Green Fluorescent Protein. Support may also be found in the description of the Virus preparation (A-5) pages 36-37. Moreover, claims 1 and 35 have been amended to clarify the genes which can be used as an

index, *i.e.*, LacZ and EGFP genes. Support may be found on page 13, lines 5-10 of the instant specification.

Claims 1, 20 and 35 have been amended to replace the term "normal differentiated cells" with the "adult normal cells." Support may be found throughout the instant specification.

No new matter has been introduced by these amendments. Reconsideration and withdrawal of the pending rejections in view of the above claim amendments and below remarks are respectfully requested.

Withdrawn Rejections

Applicants acknowledge the withdrawal of rejections to claims 1, 6, 7, 9-13 18, 20, , 21, 23-26, 35 and 36 under 35 U.S.C. §112, second paragraph as being indefinite; to claim 21 under 35 U.S.C. §112, second paragraph as being incomplete for omitting essential steps; to claims 1, 3, 4, 6-13, 18, 20, 21, 23-26, 35, and 36 under 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement, to claims 1, 6, 7, 9-13, 18, 20, 21, 23-26, 35, and 36 under 35 U.S.C. §112, first paragraph as introducing new matter, to claims 1, 6, and 7 under 35 U.S.C. §103(a) as being unpatentable over Martuza, et al., (U.S. Patent No. 5,728,379, of record) in view of Yamamura, et al., (*Cancer Research*, 61:3969-3977, 2001) and further in view of Chung, et al., (*J. Virol*, 73:7556-7564, 1999), to claims 1, 6, 7, 16-18, 20, 25, and 26 under 35 U.S.C. §103(a) as being unpatentable over Chung, et al. in view of Yamamura, et al., to claims 1, 6, 7, 16-18, 20, and 23-26 under 35 U.S.C. §103(a) as being unpatentable over Chung, et al. in view of Yamamura, et al. and further in view of Tjuvajev, et al. (*Cancer Research*, 58:4333-

4341, 1998), and to claims 1, 6, 7, 18, 20, 21, 25, and 26 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Chung, et al. in view of Yamamura, et al. and further in view of Van Meir, et al, (PGPUB 2005/0074430) and Miyatake, et al., (*Stroke*, 30:2431-2439, 1999).

Response to Provisional Non-Statutory Double Patenting Rejection

Claims 1, 6 and 7 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 10/477,797 (Publn. No. 2004-0197308) in view of Martuza (U.S. Patent No. 5,728,379, of record) and Yamamura (*Cancer Research*, 61:3969-3977, 2001; of record). Since the conflicting claims have not in fact been patented, this is a provisional obviousness-type double patenting rejection. The Examiner maintains that the rejection will be maintained until a Terminal Disclaimer is filed or claims are amended to obviate the rejection.

In response, applicants respectfully request that the provisional double-patenting rejection be held in abeyance due to the provisional nature of the rejection until one of the applications is allowed. Upon notice of otherwise allowable subject matter, applicants will address the rejection. Applicants note that it is proper when dealing with otherwise allowable subject matter in co-pending applications to withdraw a provisional rejection in the most advanced application, allow it to issue, and make a (non-provisional) rejection in the remaining application.

Response to Rejections under 35 U.S.C. §112, first paragraph – Enablement

Claims 1, 6, 7, 9-13, 18, 20, 21, and 23-26 stand rejected under 35 U.S.C. §112, first paragraph for an alleged lack of enablement. Specifically, the Examiner contends that the specification, while being enabling for an HSV vector comprising SEQ ID NO: 3 operably linked to an ICP4 gene and a TK gene, allegedly does not provide enablement for any other vector comprising SEQ ID NO: 1 or SEQ ID NO: 2 (Office Action – page 5). Applicants respectfully disagree.

However, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have amended claim 1 to recite "a region containing a full-length promoter of the human calponin gene" which is defined by the nucleotide sequence of SEQ ID NO.: 3," which as acknowledged by the Examiner is enabled (Office Action – page 5).

Claims 35 and 36 are rejected under 35 U.S.C. §112, first paragraph for lack of enablement. Specifically, the Examiner contends that the specification, while being enabling for a method of producing a cell-specific HSV vector by using the full length human calponin promoter, allegedly does not provide enablement for a method of producing a cell-specific HSV vector by using a promoter of the human calponin gene (Office Action – page 8). Applicants respectfully disagree.

However, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have amended claim 35 to recite "full length promoter of the human calponin gene," which is enabled as noted by the Examiner (Office Action – page 8).

In view of the above claim amendments, applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112, first paragraph rejection of claims 1, 3, 4, 6-13, 18, 20-34, 35, and 36.

Response to Rejections under 35 U.S.C. §112, first paragraph – New Matter

Claims 1, 3, 4, 6-13, 18, and 20-34 stand rejected under 35 U.S.C. §112, first paragraph for an alleged lack of written description. Specifically, the Examiner contends that the specification allegedly does not provide support for the phrase "normal differentiated cells," while only supporting the phrase "adult normal cells." Accordingly, the Examiner contends that such a recitation adds new matter (Office Action – pages 6-7). Applicants respectfully disagree.

However, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have amended claims 1 and 20 to replace "normal differentiated cells" with "adult normal cells," which has ample support in the specification as filed, for instance page 14, 1st paragraph.

Reconsideration and withdrawal of the enablement rejection of claims 1, 3, 4, 6-13, 18, and 20-34 under 35 U.S.C. §112, first paragraph are respectfully requested in view of amendments and claim cancellations.

Response to Rejections under 35 U.S.C. §103(a) over Martuza in view of Yamamura and Chung

Claims 1, 6, 7, 18, 20, 21, 25, 35, and 36 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Martuza, et al., (U.S. Patent No. 5,728,379) in view of

Yamamura, et al., (*Cancer Research*, 61:3969-3977, 2001) and further in view of Chung, et al., (*J. Virol*, 73:7556-7564, 1999).

According to the Examiner, Martuza allegedly teaches an HSV vector with a cell-specific promoter that drives the expression of ICP4 and the intact TK (thymidine kinase) gene (Office Action – page 11). Furthermore, the Examiner contends that Martuza teaches a method of expressing a gene in tumor cells using the HSV vector, where the HSV vector does not replicate in adult normal cells. However, the Examiner admits that Martuza does not teach the full length calponin promoter, the 4F2 enhancer or the process of inserting the DNA fragment into the ribunucleotide reductase locus. Chung and Yamamura are combined with Martuza for these alleged teachings. Specifically, Chung allegedly discloses the insertion of a tissue specific promoter operably linked to a gene into the ribonucleotide reductase locus. Whereas, Yamamura, allegedly, teaches the human calponin promoter that drives the expression of the ICP4 gene and the 4F2 enhancer (Office Action – page 14). Applicants respectfully disagree.

Applicants assert that contrary to the Examiner's contention, the claimed invention is not made obvious by the combination of Martuza, Yamamura and Chung. Martuza teaches an HSV vector with DNA construct that has a tissue specific promoter and ICP4 gene inserted in a thymidine kinase locus, which resuts in an inactive TK gene. However, because the vector does not have the TK gene, the vector would not be applied in a clinical environment due to safety issues. Whereas, if the vector contains the TK gene, it is sensitive to ganciclover and acyclovir (see paragraphs 76 and 77 of the published specification). Therefore, TK-deleted recombinants can easily be identified and selected by culturing the HSV vectors on a medium that contains ganciclover and acyclovir. To arrive at the claimed invention, the Examiner looks to Yamamura for support of a construct of a calponin promoter and ICP4 gene, which also

inserted in the TK locus and Chung for support of inserting a tissue-specific promoter and ICP4 gene construct within the ribonucleotide reductase gene locus. Assuming *arguendo* that the teachings of Martuza, Yamamura and Chung could be combined as suggested by the Examiner, one skilled in the art would still not arrive at the claimed invention.

The Examiner's attention is directed to the fact that the claimed HSV vector is obtained by inserting a DNA fragment comprising the region containing a full length promoter of the human calponin gene, the ICP4 gene, and two marker genes – the LacZ (marker) gene and the EGFP (marker) gene into the ribonucleotide reductase (RR) gene locus. Applicants respectfully point out that by using the claimed DNA fragment, the altered HSV vector can be identified because this cDNA expresses a green fluorescent protein (EGFP) that shows fluorescence. Whereas, Martuza, Chung and Yamamura alone or in combination does not teach each and every element of the claimed invention, *i.e.*, a DNA fragment comprising two specific marker genes – the LacZ (marker) gene and the EGFP (marker) gene inserted within the RR locus. In fact, Martuza and Yamamura utilize the inactivation of TK gene as a marker or index, whereas Chung utilizes the removal of the LacZ gene from RR locus as a marker or index. Thus, even in combination, the cited art would not produce the claimed HSV vector that has a full length promoter of the human calponin gene, the ICP4 gene, and two marker genes – the LacZ (marker) gene and the EGFP (marker) gene inserted in the ribonucleotide reductase (RR) gene locus.

Furthermore, applicants assert that one skilled in the art could not combine the teachings of Martuza and Yamamura with Chung without a great deal of undue experimentation. Martuza produced a cell-specific expression replication vector ptkΔL-ALI4 where a DNA fragment coupling ICP4, albumin promoter and lacZ is inserted into the thymidine kinase (TK)

gene locus by homologous recombination (*i.e.*, tumor cell-specific proliferation due to TK ablation; liver tumor cell-specific proliferation due to ICP4 expression by albumin promoter). Martuza, however, did not succeed in producing a cell-specific expression replication vector where a DNA fragment coupling ICP4, albumin promoter and lacZ is inserted into the ribonucleotide reductase (ICP6) gene locus by homologous recombination. Martuza produced only the replicable HSV-1 vector G207 which lacks copies of the γ34.5 gene involved in replication in neural cells and in which only LacZ gene is inserted in the ribonucleotide reductase (ICP6) gene locus (tumor cell-specific proliferation due to TK ablation; non cell-specific due to lack of ICP4 gene coupling to a cell-specific promoter).

Chung, on the other hand, describes a predetermined viral gene γ34.5 that can be combined with the B-myb promoter and inserted within the RR gene locus. Chung does not teach how to insert other tissue-specific promoters, *e.g.*, albumin promoter of Martuza, in conjunction with the ICP4 gene and LacZ. Applicants assert that the construct of Martuza, *i.e.*, ICP4, albumin promoter and lacZ, is not the same as the construct of Chung, *i.e.*, viral gene γ34.5 and B-myb promoter, and are not interchangeable as suggested by the Examiner. Applicants respectfully assert that one skilled in the art could not make a construct of Martuza within the RR locus as taught by Chung without significant attempts because any one of the lacZ gene, a cell-specific promoter, and an ICP4 gene may undergo ablation when attempting to construct a herpes viral vector as claimed, or because of the difficulty in cloning the vector even when such a vector with appropriate recombination of the above three elements has been produced.

Therefore, none of the references, either alone or in combination, discloses all the elements to produce the claimed HSV vector and one skilled in the art would not look to Chung

to overcome the deficiencies of Martuza and Yamamura. Reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) of the claims 1, 6, 7, 18, 20, 21, 25, 35, and 36 are respectfully requested in view of claim amendments and for the above reasons.

Response to Rejections under 35 U.S.C. §103(a) over Martuza, in view of Chung, Yamamura and Van Meir

Claims 1, 6, 7, 9-13, 18, 20, 21, 25, 35, and 36 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Martuza, et al. in view of Yamamura, et al. and Chung, et al. and further in view of Van Meir, et al, (PGPUB 2005/0074430). Specifically, claims 1, 6, 7, 9-13, 18, 20, 21, 25, 35, and 36 stand rejected over Martuza, Yamamura and Chung, while claims 9-13 are allegedly made further obvious in view of Van Meir. Applicants respectfully disagree.

However, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have cancelled claims 9-13. Therefore, the rejection to these claims is now moot.

Response to Rejections under 35 U.S.C. §103(a) over Martuza, in view of Chung and Yamamura and further in view of Miyatake

Claims 1, 6, 7, 18, 20, 21, 25, 26, 35, and 36 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Martuza, et al. in view of Yamamura, et al. and Chung, et al. and further in view of Miyatake, et al., (*Stroke*, 30:2431-2439, 1999). According to the

Examiner, Martuza, Yamamura and Chung teach the claimed invention as recited in claims 1, 6, 7, 20, 21, 25, 35, and 36 except they do not teach a therapy by targeting the virus to proliferating smooth muscle cells, an element of claims 18 and 26, which is allegedly made obvious by Miyatake. Applicants respectfully disagree.

Applicants respectfully assert that Martuza in view of Yamamura and Chung do not teach each and every element of the claimed invention. Moreover, the addition of Miyatake does not remedy the deficiencies of the combination of Martuza Yamamura and Chung.

Furthermore, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have cancelled claim 18. Therefore, the rejection to this claim is now moot.

Applicants assert that the combination of Martuza, Yamamura, Chung and Miyatake does not teach, disclose, or suggest the DNA fragment claimed in claim 1. Specifically, applicants respectfully assert that Miyatake does not cure the deficiencies of Martuza noted in the previous subsection even in combination with Yamamura and Chung, *i.e.*, a DNA fragment comprising the region containing a promoter of the full length human calponin gene, the ICP4 gene, and two marker genes – the LacZ (marker) gene and the EGFP (marker) gene. Thus, applicants contend, that the proposed combination of references fails to teach, disclose, or suggest all of the claim elements of applicant's invention, *i.e.*, the LacZ (marker) gene and the EGFP (marker) gene. For at least these reasons, reconsideration and withdrawal of the rejections of the claim 26 are respectfully requested.

Response to Rejections under 35 U.S.C. §103(a) over Martuza in view of Chung, Yamamura and Tjuvajev

Claims 1, 6, 7, 18, 20, 21, 23-25, 35, and 36 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Martuza, et al. in view of Yamamura, et al. and Chung, et al. and further in view of Tjuvajev, et al. (Cancer Research, 58:4333-4341, 1998). According to the Examiner, Martuza, Yamamura and Chung teach the claimed invention as disclosed in claims 1, 6, 7, 18, 20, 21, 25, 35, and 36 except they do not teach detecting the in vivo distribution of the vector by determining tk activity using PET and FIAU labeled with ^{124}I of instant claims 23 and 24, which is allegedly made obvious by the disclosure of Tjuvajev. Applicants respectfully disagree.

Applicants assert that the combination of Martuza, Yamamura, Chung and Tjuvajev does not teach, disclose, or suggest the DNA fragment claimed in claim 1. Specifically, applicants respectfully assert that Tjuvajev does not cure the deficiencies of Martuza noted in the previous subsection even in combination with Yamamura and Chung, *i.e.*, a DNA fragment comprising the region containing a promoter of the full length human calponin gene, the ICP4 gene, and two marker genes – the LacZ (marker) gene and the EGFP (marker) gene. Thus, applicants contend, that the proposed combination of references fails to teach, disclose, or suggest all of the claim elements of applicant's invention, *i.e.*, the LacZ (marker) gene and the EGFP (marker) gene. For at least these reasons, reconsideration and withdrawal of the rejections of the claims 23 and 24 are respectfully requested.

Dependent Claims

The applicants have not independently addressed all of the rejections of the dependent claims. The applicants submit that for at least similar reasons as to why independent claims 1 and 35 from which all of the dependent claims 6, 7, 20-21, 23-26, and 36 depend are believed allowable as discussed *supra*, the dependent claims are also allowable. The applicants however, reserve the right to address any individual rejections of the dependent claims and present independent bases for allowance for the dependent claims should such be necessary or appropriate.

Thus, applicants respectfully submit that the invention as recited in the claims as presented herein is allowable over the art of record, and respectfully request that the respective rejections be withdrawn.

CONCLUSION

Based on the foregoing amendments and remarks, the applicants respectfully request reconsideration and withdrawal of the pending rejections and allowance of this application. The applicants respectfully submit that the instant application is in condition for allowance. Entry of the amendment and an action passing this case to issue is therefore respectfully requested. In the event that a telephone conference would facilitate examination of this application in any way, the Examiner is invited to contact the undersigned at the number provided. Favorable action by the Examiner is earnestly solicited.

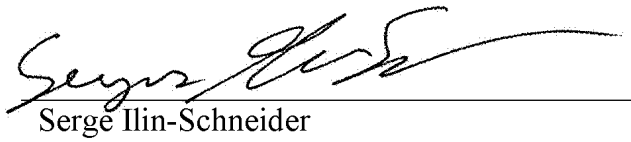
AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **13-4500**, Order No. 4439-4022.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **13-4500**, Order No. 4439-4022.

Respectfully submitted,
MORGAN & FINNEGAN, L.L.P.

Dated: April 3, 2008

By: 
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